Received: 18 May 2019 | Revised: 4 October 2019 | Accepted: 16 October 2019

DOI: 10.1111/bcp.14164

SYSTEMATIC REVIEW AND META-ANALYSIS

BJCP BRITISH PHARMACOLOGICAL SOCIETY

Impact of the pharmacist-led intervention on the control of medical cardiovascular risk factors for the primary prevention of cardiovascular disease in general practice: A systematic review and meta-analysis of randomised controlled trials

Abdullah A. Alshehri[1,2] | Zahraa Jalal[1] | Ejaz Cheema[1] | M. Sayeed Haque[3] | Duncan Jenkins[4] | Asma Yahyouche[1]

[1]School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK

[2]Clinical Pharmacy Department, College of Pharmacy, Taif University, Al Huwaya, Taif, Saudi Arabia

[3]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

[4]Morph Consultancy Ltd, Worcester, UK

Correspondence
Abdullah Alshehri, School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham. UK.
Email: aaalshehri2@hotmail.com

Aims: To conduct a systematic review and meta-analysis of the effectiveness of general practice-based pharmacist interventions in reducing the medical risk factors for the primary prevention of cardiovascular events.

Methods: A systemic search was undertaken in 8 databases: PubMed, MEDLINE, EMBAS, PsycINFO, Cochrane Library, CINAHL Plus, SCOPUS and Science Citation Index, with no start date up to 27 March 2019. Randomised controlled trials assessing the effectiveness of pharmacist-led interventions delivered in the general practice in reducing the medical risk factors of cardiovascular events were included in the review. The risk of bias in the studies was assessed using the Cochrane risk of bias tool.

Results: A total of 1604 studies were identified, with 21 randomised controlled trials (8933 patients) meeting the inclusion criteria. Fourteen studies were conducted in patients with diabetes, 7 in hypertension, 2 involving dyslipidaemia, and 2 with hypertension and diabetes together. The most frequently used interventions were medication review and medication management. The quality of the included studies was variable. Patients receiving pharmacist-led interventions were associated with a statistically significant reduction in their systolic blood pressure (−9.33 mmHg [95% Confidence Interval (CI) −13.36 to −5.30]), haemoglobin A1C (−0.76% [95% CI −1.15 to −0.37]) and low-density lipoprotein–cholesterol (−15.19 mg/dL [95% CI −24.05 to −6.33]). Moreover, practice-based pharmacists' interventions were also reported to have a positive impact on patient adherence to medications.

Conclusion: The findings of this review suggest that pharmacist-led interventions in general practice can significantly reduce the medical risk factors of cardiovascular disease events. These findings support the involvement of pharmacists as healthcare providers in managing patients with hypertension, diabetes and dyslipidaemia.

KEYWORDS

cardiovascular disease, general practice, pharmacist

PI statement: The authors confirm that the Principal Investigator for this paper is Abdullah A. Alshehri and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Cardiovascular disease (CVD) continues to be a leading cause of death and disability-adjusted life years (DALY) worldwide accounting for nearly 18 million deaths per year (31% mortality rate)[1] with an estimated 150 million DALYs by the year 2020.[2] For example, in the year 2015 alone, CVD was responsible for around 3.9 million deaths (45%) of all reported deaths in Europe and around 65 million DALYs.[3] The European Heart Network estimates that the total cost attributable to CVD in Europe is €210 billion per year, while the cost attributed to the UK economy is around €22 billion per year.[3]

Numerus studies including Framingham heart study[4] and the INTERHEART study[5] identified the modifiable and nonmodifiable risk factors of CVDs. The INTERHEART study conducted in the year 2004 outlined the effects of modifiable risk factors of CVD including hypertension (HTN), diabetes mellitus (DM), hyperlipidaemia, smoking, alcohol consumption, high body mass index, psychosocial conditions, unhealthy diet and irregular exercise.[5] These 9 modifiable risk factors can potentially reduce the risk of acute myocardial infarction by 90%. Early detection, intervention and management of these risk factors, are among some of the primary prevention strategies that can reduce the burden of CVD worldwide.

The Alma-Ata Declaration (1978) mentioned the primary health care as the key to achieve the goal of "Health for All".[6] General practice (GP) is the primary and most common point of contact for individuals with health care needs especially in the developed countries. For example, in the UK, GP has been considered as the jewel in the crown of the National Health Service.[7] However, over the past few years, GP has faced increased workload due to multiple reasons including the increase in population and average lifespan, increased prevalence of long-term medical conditions, frequency of diseases and complexity of treatment regimen.[8] Pharmacists by virtue of patient education, medicine reconciliation and management of CVD risk factors can play an important role in the primary prevention of CVD[9] that can help ease the burden on primary care physicians (PCP).

Several systematic reviews and meta-analysis have assessed the effectiveness of pharmacists' led interventions in reducing the risks associated with CVD across a range of healthcare settings.[10-14] However, these reviews were largely limited to interventions by community or hospital pharmacists with no assessment of pharmacist interventions in general practice. A systematic review and meta-analysis that assessed the impact of pharmacist's services on patients with primary and secondary prevention diseases in general practice conducted in the year 2014.[15] However, this review included services provided by pharmacists' alone or in collaboration with the PCP and other health care providers. Furthermore, several randomised controlled trials (RCTs) have been conducted to assess the pharmacist-led interventions since the publication of that review. This review therefore, aims to assess the impact of pharmacists' interventions focusing on the medical risk factors for the primary prevention of cardiovascular events in general practice by limiting the analysis to RCTs and by standardising the type of interventions used by pharmacists.

What is already known about this subject

- Hypertension, diabetes and dyslipidaemia are significant medical risk factors that can lead to cardiovascular disease (CVD), which continues to be a leading cause of death and disability-adjusted life years worldwide
- Evidence suggests that pharmacists play an important role in the management of chronic diseases such as CVD

What this study adds

- This systematic review and meta-analysis limited to randomised controlled trials provides evidence that pharmacist-led interventions can make a clinically important contribution in the primary prevention of CVD in the general practice
- The pharmacist-led interventions not only improved patients medicine adherence but were also reported to be cost-effective

2 | METHODS

The protocol was registered prospectively on PROSPERO (registration no CRD42018107132). The review supports the PRISMA statement[16] as well as the Joanna Briggs Institute (JBI) methods.[17]

2.1 | Search strategy

A systemic search of the literature was undertaken by AA using 8 electronic databases: PubMed (NCBI), Ovid MEDLINE (1946), EMBASE (1974), PsycINFO (OVID) (1967), Cochrane Library (Wiley), CINAHL Plus (EBSCO) (1937), SCOPUS (ELSEVIER) and Science Citation Index Expanded (Web of Science Core Collection) (1900) from inception to 27 March 2019. Some of the key words included: "pharmacist", "general practice", "cardiovascular diseases", "hypertension", "diabetes" and "dyslipidaemia". All terms in each database combined with Boolean operators (AND, OR and/or NOT). Searches were restricted to the English language and randomised controlled trials or cluster randomised controlled trials (See Appendix S1 for Search strategy). In addition, reference lists of included studies were screened to identify any additional relevant studies.

2.2 | Types of study

Studies were included in this review if they were RCTs or cluster RCTs that assessed the effectiveness of pharmacists' interventions delivered in general practice. Studies were included if they had compared pharmacists' interventions with usual care. Studies were

excluded if they assessed pharmacists' interventions for cardiovascular disease prevention including post-stroke, myocardial infarction or heart failure. Studies were also excluded if they were delivered in community pharmacies, ambulatory units, secondary or tertiary care settings. Furthermore, studies that assessed pharmacists' interventions in collaboration with other healthcare were also excluded.

2.3 | Types of participant

Studies of adult patients (age ≥18 years) with at least 1 of the medical risk factors for the primary prevention of cardiovascular disease, mainly HTN, type 2 DM and dyslipidaemia were eligible for inclusion.

2.4 | Types of intervention

Patient education, medication review and counselling, physical assessment, assessing adherence, lifestyle modification, and medication management such as prescribing, adjusting, monitoring and administering therapy, and identifying drug-related problems.

2.5 | Outcomes assessed

2.5.1 | Primary outcomes

The primary outcomes assessed included changes in systolic–diastolic blood pressure (SBP, DBP), haemoglobin A1C (HbA1c), fasting blood glucose (FBG), lipid profiles and cardiovascular risk score.

2.5.2 | Secondary outcomes

The secondary outcomes assessed medicine adherence and cost effectiveness of pharmacists' interventions in general practice.

2.6 | Study selection and data extraction

All the initially identified studies were uploaded to Rayyan QCRI (a web and mobile app for a systematic review screening that facilitates collaboration between different reviewers for inclusion and exclusion of studies).[18] Using this app, 2 reviewers (A.A. and A.Y.) independently screened titles and abstracts of all potentially relevant papers based on the selection criteria. Then the full text of eligible studies was screened for inclusion by each reviewer. Any disagreements about study inclusion were resolved by the involvement of a third reviewer (Z.J.). Reviewer A.A. independently extracted data from included studies using a data extraction sheet (See Appendix S2 for characteristics of included studies). Reviewer A.Y. checked all data extracted in the sheets. The data extracted included: study design; country and setting; primary outcomes; assessed population size; patient age and sex; duration of intervention and follow up; and study results.

2.7 | Risk of bias assessment

The risk of bias in the included studies was assessed by 2 independent reviewers (A.A. and E.C.) using the Cochrane Handbook risk of bias assessment tool.[19] Each study was assessed according to the following criteria: method of randomisation, concealment of allocation, blinding of outcome assessors, addressing of incomplete outcome data, selective outcome reporting and other sources of bias. Each risk of bias item was rated as *low risk*, *unclear* or *high risk*. A risk of bias graph and risk of bias summary was produced to report the quality of included studies. (See Appendix S3 for the risk of bias assessment tool).

2.8 | Statistical analysis

A meta-analysis was conducted using Review Manager (RevMan, Version 5.3) for all primary outcome measures except cardiovascular risk score and FBG due to insufficient studies assessing these outcomes. For continuous outcomes, data extracted from these studies included sample size, means and standard deviations. If these were not reported, standard deviations from confidence intervals (CIs) were obtained where possible. We included final score data, in the absence of final score data, difference in the baseline and follow up score was used in the meta-analyses, following the advice of the *Cochrane Handbook9.4.5.2*.[19] Secondary outcomes were not included in the meta-analysis due to variations in the measurement of study outcomes including patient medication adherence and the cost-effectiveness tools. These outcomes were included in the narrative review.

A random-effects model was used to synthesise the data due to the expected heterogeneity between included studies. To further minimise heterogeneity, studies using similar interventions (medication review and medication management) were included in meta-analysis. Heterogeneity was measured using χ^2 tests and the I^2 statistic. A heterogeneity above 50% was considered *substantial* heterogeneity and above 75% was considered as considerable heterogeneity.[19] The effect size was calculated as the mean difference with 95% CI. A meta-regression was conducted to examine relationship between the magnitudes of the difference in all the outcome measures used in the meta-analysis with the duration of studies. The statistical package STATA (Version 16) was used for this part of the analysis.

3 | RESULTS

3.1 | Search and study selection

The initial search produced 1,604 studies (Figure 1 shows the PRISMA flow diagram for this study[16]). After removal of duplicates and studies

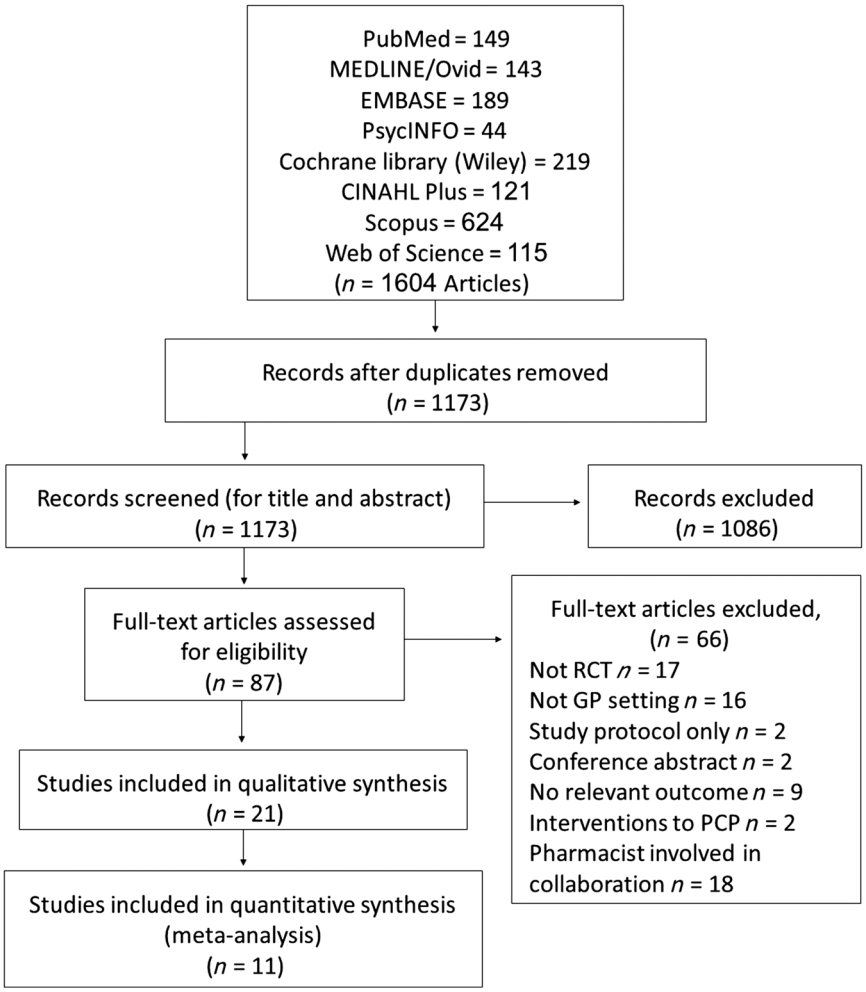

FIGURE 1 Flow diagram of study selection process. RCT, randomised controlled trial; GP, general practice; PCP, primary care physician

that did not match the inclusion criteria, 1173 were searched at title and abstract level. Of these studies, 1086 were excluded, 87 studies were deemed eligible for full-text screening. Sixty-six studies were subsequently excluded because of study design, interventions not located in general practice setting, study protocol, conference abstract, no relevant outcome, interventions provided to primary healthcare physician and/or the pharmacist involved in collaboration with other healthcare providers. Finally, 21 RCTs contributed to the systematic review.[20-40] Of these, 11 studies were included in the meta-analysis.

3.2 | Study characteristics

The 21 studies included involved 8933 participants aged from 49 to 65 years. The included studies were either cluster randomised controlled trials[23,26,27] or were randomised controlled trials[20-22,24,25,28-40] conducted in general practice. The studies were conducted in different countries including: 10 in USA,[21,23,24,26,27,31-34,40] 4 in Canada,[22,25,35,36] 3 in Brazil,[28-30] and 1 each in Jordan,[38] Chile,[39] Malaysia[20] and Thailand.[37] Appendix S2, presents further characteristics of the studies included in this systematic review. Of the 21 included studies, 14 were included patients with diabetes,[20-25,28-30,32-36] 7 with hypertension[26,27,29-31,37,40] and 2 with dyslipidaemia.[38,39] Pharmacists used multifaceted interventions including patient education, medication review and counselling, physical assessment (e.g. BP), assessing adherence, lifestyle modification, and medication management such as prescribing, adjusting, monitoring and administering therapy and identifying drug related problems. The duration of the interventions ranged from 3[34] to 36 months.[29]

3.3 | Study quality

The quality of the included studies was variable (see Figure 2 for risk of bias graph). Five studies (25%) did not report blinding of outcome assessed and 2 studies (10%) had attrition bias. Appendix S3, presents the risk of bias summary for each study.

3.4 | Meta-analysis

Eleven RCTs included in the meta-analysis (2253 patients) used 2 similar interventions, medication review and medication management.[20,21,26,28,29,31,32,35,37,39,40] Only 1 trial[34] that measured clinical endpoints was excluded, as appropriate data were not available.

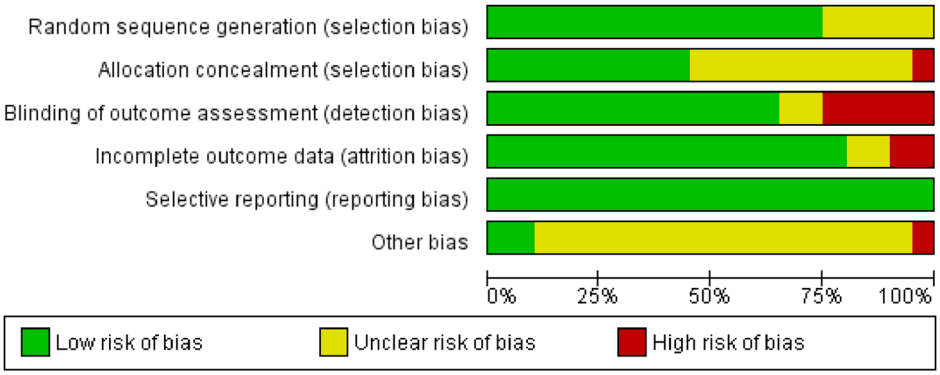

FIGURE 2 Risk of bias graph: the review authors' judgments about each risk-of-bias item presented as percentages across all included studies

3.5 | Impact of pharmacist-led interventions on blood pressure

Of the 11 RCTs included in the meta-analysis, 9 studies (1841 patients) reported both SBP and DBP.[20,26,28,29,31,32,35,37,40]

3.5.1 SBP

Meta-analysis of data from the 9 studies reported a significant reduction in favour of intervention participants, with a pooled effect of 9.33 mmHg reduction in SBP (95% CI −5.30 to −13.36, Z = 4.54; $P < .0001$) using the random effect model. There was considerable heterogeneity among studies assessing SBP (χ^2 = 56.04, df = 8; $P < .0001$; I^2 = 86%, Figure 3A). The major heterogeneity could be attributed to the inclusion of a study with a longer duration of follow-up (3 years)[29] compared to the other studies that used between 6–12 months of follow-up period.

3.5.2DBP

Meta-analysis of data from the 9 studies showed statistical significant reduction in favour of practice pharmacist interventions, with a pooled effect of 3.71 mmHg reduction in DBP (95% CI −1.43 to −6.00, Z = 3.18; $P = .001$) using the random effect model. Statistical heterogeneity across the studies assessing DBP was considerable (heterogeneity: χ^2 = 38.41, df = 8; $P < .0001$; I^2 = 79%, Figure 3B).

3.6 | Impact of pharmacist-led interventions on blood glucose

Of the 11 RCTs included in the meta-analysis, 5 studies (694 patients) reported HbA1c.[20,21,28,29,35] Meta-analysis of data from the 5 studies showed statistical significant reduction in favour of practice pharmacist interventions, with a pooled effect of 0.76% greater reduction in HbA1c (95% CI −0.37 to −1.15, Z = 3.81; $P = .0001$) when compared

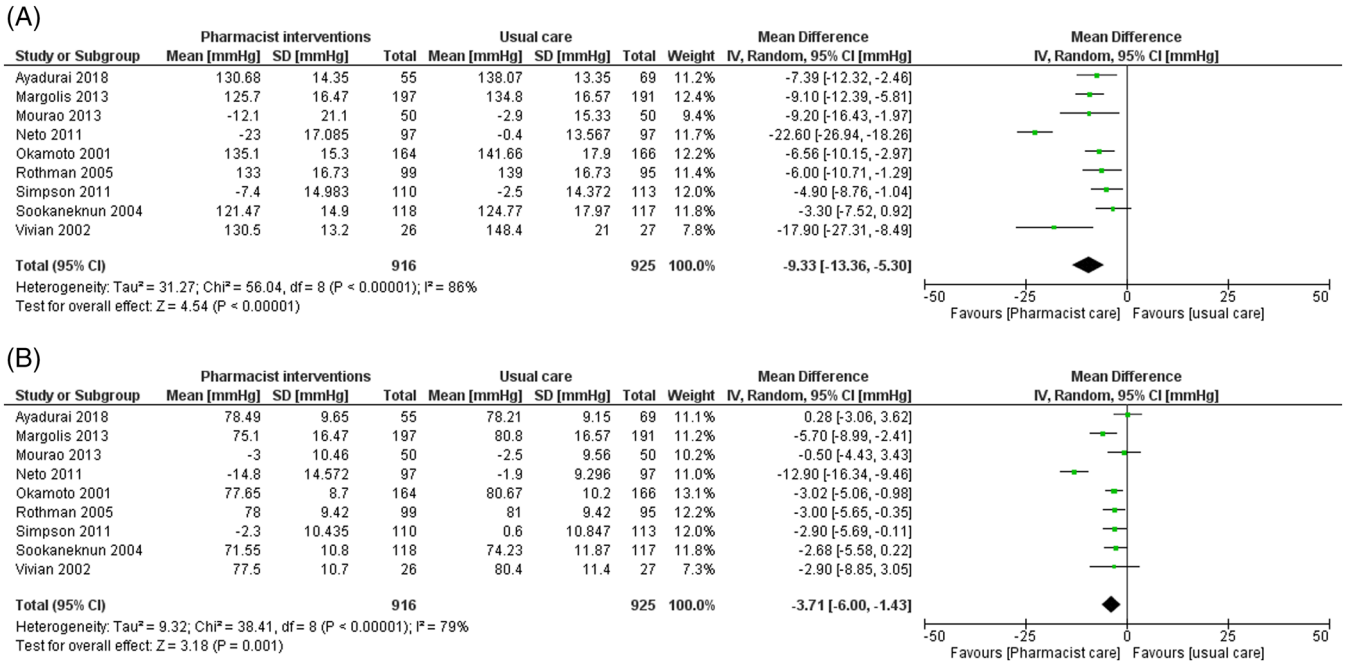

FIGURE 3 Forest plots show the effect of pharmacist intervention on the mean difference in systolic blood pressure (A) and in diastolic blood pressure (B)

to usual care. There was considerable heterogeneity among studies assessing HbA1c (χ^2 = 13.97, df = 4; P = .007; I^2 = 71%, Figure 4). Only 2 RCTs in this review THAT measured FBG (441 patients)[28,29] demonstrated statistically significant reduction in favour of pharmacist care.

3.7 | Impact of pharmacist-led interventions on lipid profiles

Five RCTs reporting data on clinical outcomes of dyslipidaemia were included in the meta-analysis.[20,28,29,35,39]

3.7.1 | Total cholesterol

Meta-analysis of these 5 studies assessing total cholesterol (TC; 752 patients) indicated statistically significant reductions in favour of the practice pharmacist care, and the pool estimate showed a significant reduction in TC (−20.24 mg/dL [−33.53, −6.95], Z = 2.99; P = .003). There was considerable heterogeneity among studies assessing TC (χ^2 = 22.36, df = 4; P = .0002; I^2 = 82%, Figure 5A).

3.7.2 | Low-density lipoprotein—cholesterol

Meta-analysis of the 5 RCTs assessing low-density lipoprotein–cholesterol (LDL-C; 738 patients) showed statistical significant reduction in favour of pharmacist care, with a pooled effect of 15.19 mg/dL reduction in LDL-C (95% CI −6.33 to −24.05, Z = 3.94; P = .0008). Statistical heterogeneity across the studies assessing LDL-C was substantial (χ^2 = 11.79, df = 4; P = .003; I^2 = 66%, Figure 5B).

3.7.3 | High-density lipoprotein–cholesterol

Meta-analysis of 5 studies that reported high-density lipoprotein–cholesterol (HDL-C; 742 patients, see Figure 5C), the pooled estimate did not show a statistically significant change in HDL-C (4.56 mg/dL [−0.62, 9.75], Z = 1.73; P = .08). There was considerable heterogeneity among studies assessing HDL-C (χ^2 = 72.32, df = 4; P < .0001; I^2 = 94%).

3.7.4 | Triglyceride

Five studies reporting changes in triglyceride levels (753 patients) demonstrated statistically significant reduction in favour of pharmacist care. Pooled analyses of pharmacist interventions indicated a −37.90 mg/dL greater reduction in triglyceride (95% CI −16.98 to 58.81, Z = 3.55; P = .0004) when compared to usual care. There was substantial heterogeneity (χ^2 = 8.08, df = 4; P = .09; I^2 = 50%, Figure 5D) among studies assessing triglyceride in the meta-analysis.

3.8 | Sensitivity analysis

Two approaches were used to measure the robustness of the results. Firstly, studies with <6 months of follow-up were excluded from the meta-analysis. Secondly, as recommended by Tobias,[41] studies were excluded stepwise to assess the overall input on Z-statistic and P value. Both approaches did not make any significant difference in the results of any outcomes of meta-analysis.

3.9 | Meta-regression

The meta-regression revealed a statistically significant negative relationship between the magnitude of the difference in both SBP (P < .001) and DBP (P < .001) with the duration of studies. This means that the longer the duration of the study the smaller is the difference in both SBP and DBP. All other outcome measures did not reveal any statistically significant association with the duration of studies.

3.9.1 | Cardiovascular risk score

Cardiovascular risk score was estimated in 2 studies.[25,29] The Framingham Risk Score (FRS) was used in both studies to predict CHD

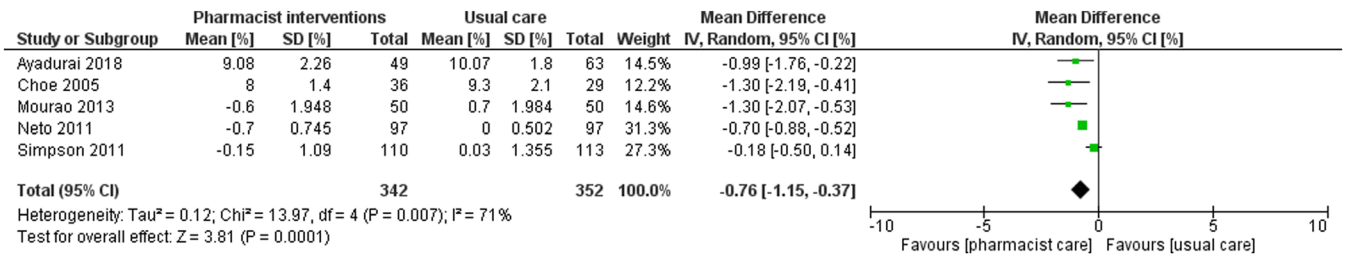

FIGURE 4 Forest plots show the effect of pharmacist intervention on the mean difference in haemoglobin A1C

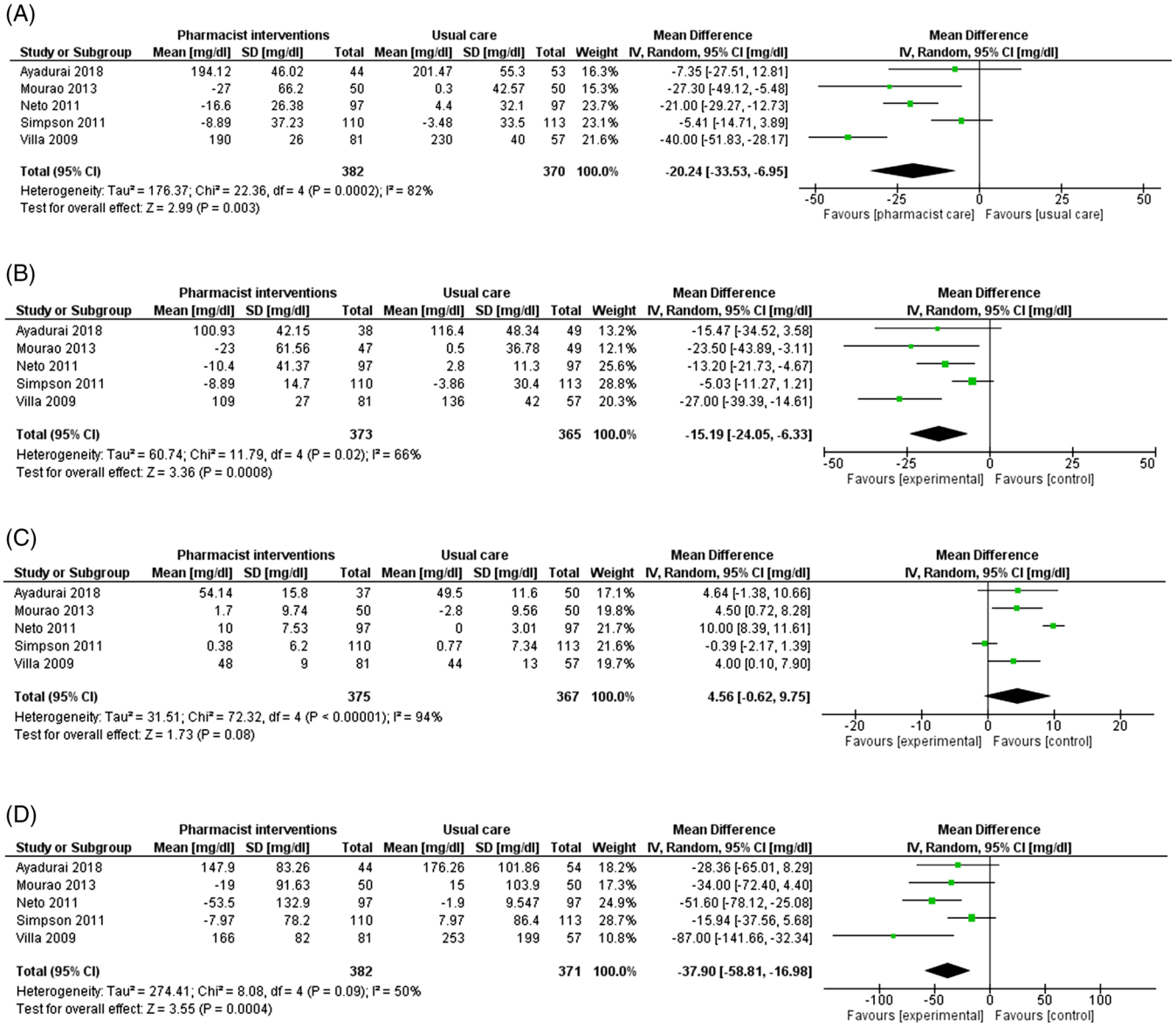

FIGURE 5 Forest plots show the effect of pharmacist intervention on the mean difference in Total cholesterol (A), low-density lipoprotein–cholesterol (B), high-density lipoprotein–cholesterol (C) and in triglyceride (D), in pharmacist and usual care groups show an

risk. There was a significant reduction in mean FRS in the intervention group and a significant difference in the change in comparison to the control group.[29] Ladhani *et al.*[25] demonstrated a significant decrease in median change of FRS in intervention patients, but no significant difference in median change comparison with the control group.

3.9.2 | Medication adherence

Nine RCTs assessed patient's adherence to their medication.[20,23,24,26,28,29,37,38,40] Due to the variations in methods of measuring adherence, meta-analysis was not conducted. Methods of adherence measurement included: prescription refill, the validated Morisky–Green test (4 items scale), tablet counting and filling in self-reported questionnaires by patients were used. Three studies reported a significant increase in medication adherence in the intervention compared to the control group.[26,29,37] Two studies[28,40] reported nonstatistical significant improvement in the intervention group compared to control group. The remaining 4 studies provided no quantitative data about adherence.

3.9.3 | Cost-effectiveness analysis

Three studies analysed the cost effectiveness of the pharmacists' interventions.[30,31,36] All these studies indicated that the cost-

effectiveness ratio was lower in the intervention group than in the control group. Furthermore, these studies identified no significant difference in total direct healthcare related costs between the intervention and control groups that was associated with a statistically significant improvement on clinical outcomes.

4 | DISCUSSION

To author's knowledge, this is the first comprehensive systematic review and meta-analysis of RCTs that has focused on pharmacists' interventions on the medical risk factors for primary prevention of cardiovascular disease solely in the general practice setting. The findings of this review suggest that pharmacist's interventions directed to patients with HTN, type 2 DM or dyslipidaemia could significantly improve their clinical outcomes compared to patients without pharmacists' interventions.

The improvement in the clinical outcomes reported in this review are consistent with the findings of a previous systematic review and meta-analysis that assessed the impact of hospital and community pharmacists' interventions on CVD risk factors in diabetic patients.[42] Moreover, a recent review conducted by pharmacist across range of healthcare settings including general practice and reported a positive effect on blood pressure, HbA1c, lipid profiles and the prediction for CV risk score for diabetic patients.[43] These 2 reviews support the findings of this review were conducted in other settings besides general practice. A systematic review conducted in general practice reported a statistically significant improvement in BP, HbA1c, TC and FRS.[15] However, these interventions were delivered by pharmacists alone or in collaboration with the PCP for a range of chronic diseases. Furthermore, this review identified an additional 4 studies that was not included by Tan *et al.*[15] besides assessing clinical outcomes not assessed previously.

Studies included in this review reported improvement in medication adherence. This finding is also consistent with results from a previous systematic review,[44] which described the role of hospital and community pharmacists in management of patients with CVDs and showed statistically significant results improving adherence to prescribed medication. There was limited evidence regarding the cost effectiveness as only 3 studies conducted an economic analysis. These findings show that pharmacist interventions are greatly cost effective and limited effect on total cost between intervention and usual care groups. Future work including economic and clinical outcomes, along with humanistic outcomes (ECHO approach) should be considered in order to reach a comprehensive evaluation of pharmaceutical services.[45] A recent review of many systematic reviews assessed the impact of pharmacists' interventions on both cardiovascular medical risk factors and diseases across settings and supports findings from our review as it, indicated that both humanistic outcomes such as adherence and economic outcomes are poorly assessed in the current available literature.[9]

4.1 | Implications for practice and policy

The evidence presented in this review, together with previous reviews, provide an important message to health organisation systems and policy makers regarding the effectiveness of GP practice-based pharmacists' interventions. The review demonstrates that pharmacists have an important role in contributing to the management of chronic diseases such as diabetes and hypertension. The significant reductions in SBP, DBP, HbA1c, FBG, TC, LDL and triglyceride reported in this meta-analysis, if sustained in clinical practice, could have significant implications for managing HTN, DM and dyslipidaemia that could prevent cardiovascular morbidity and mortality. For example, evidence from a meta-analysis involving 1 million adults suggested that every 1 mmHg reduction in SBP could prevent about 10,000 deaths related to CHD in the USA each year.[46] In addition, evidence from an epidemiological analysis of the UK Prospective Diabetes Study presented that every percentage point reduction in HbA1c reduced about 25% of diabetes-related deaths and 18% of myocardial infarction.[47] Additionally, the findings of the humanistic and economic cost of pharmacist interventions would have important implication on saving the economic resources and easing the burden and financial on healthcare services.

4.2 | Strengths and limitations

The review has some limitations. Although, all the relevant studies were identified by a broad search strategy and manual checking reference lists, non-RCTs and studies published in languages other than English were not included. This review did not include nonmedical risk factors of CVD such as smoking, alcohol consumption and physical activities. Although this review addressed patient adherence to medication, other humanistic outcomes such as patient satisfaction and health-related quality of life were not included.

Additionally, while most of the studies favoured pharmacists' interventions compared with usual care, there was a considerable heterogeneity between the identified studies. Nevertheless, this review minimised the risk of heterogeneity by limiting the meta-analysis to studies using similar pharmacists' interventions (medication review and medication management) and by using 2 approaches to measure the robustness of the results.

5 | CONCLUSIONS

This systematic review suggests that pharmacist-led interventions in general practice have a significant impact on reducing the medical risk factors for primary prevention of CVD events. In addition, pharmacist interventions were effective in improving medication adherence and were cost effective. These findings support a greater involvement of the pharmacist in the general practice in the management all of HTN, DM and dyslipidaemia. Future work is needed to address the

effectiveness of pharmacist's interventions on nonmedical risk factors of cardiovascular disease such as obesity, smoking and alcohol consumption. More sustained RCTs to present the clinical, economical and humanistic outcomes on long duration of interventions are recommended.

CONTRIBUTORS

A.A., J.Z. and Y.A. conceived of the presented idea and carried out the review. J.Z.; contributed to the reviewing and writing the manuscript. E.C.; contributed to the implementation of the analysis, quality assessment and to the writing of the manuscript. H.S.; provided statistical analysis. J.D.; reviewed and feedback on the manuscript. A.A.; took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research and manuscript.

COMPETING INTERESTS

The authors report no conflict of interest.

ORCID

Abdullah A. Alshehri https://orcid.org/0000-0002-4785-4551
Zahraa Jalal https://orcid.org/0000-0002-6126-3379
Ejaz Cheema https://orcid.org/0000-0002-8538-7392
Asma Yahyouche https://orcid.org/0000-0002-3348-6399

REFERENCES

1. WHO. Cardiovascular diseases (CVDs), 2017. Available from: http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed 20 March 2018.
2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381.
3. Wilkins E, Wilson L, Wickramasinghe K, et al. *European Cardiovascular Disease Statistics 2017*. European Heart Network: Brussels; 2017.
4. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *Jama*. 1979;241(19):2035-2038.
5. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet (London, England)*. 2004;364(9438):937-952.
6. WHO. Declaration of Alma-Ata: International Conference on Primary Health Care, Alma-Ata, USSR, 6–12 September 1978. Available at: https://www.who.int/publications/almaata_declaration_en.pdf. Accessed 2019.
7. Berwick DM. A transatlantic review of the NHS at 60. *Bmj*. 2008;337(jul17 1):212-214.
8. Baird B, Charles A, Honeyman M, Maguire D, Das P. *Understanding pressures in general practice* King's Fund London; 2016.
9. Omboni S, Caserini M. Effectiveness of pharmacist's intervention in the management of cardiovascular diseases. *Open Heart*. 2018;5(1):1-14.
10. Brown TJ, Todd A, O'Malley C, et al. Community pharmacy-delivered interventions for public health priorities: a systematic review of interventions for alcohol reduction, smoking cessation and weight management, including meta-analysis for smoking cessation. *BMJ Open*. 2016;6(2):1-18.
11. Ifeanyi Chiazor E, Evans M, van Woerden H, Oparah AC. A systematic review of community Pharmacists' interventions in reducing major risk factors for cardiovascular disease. *Value in Health Regional Issues*. 2015;7:9-21.
12. Blenkinsopp A, Anderson C, Armstrong M. Systematic review of the effectiveness of community pharmacy-based interventions to reduce risk behaviours and risk factors for coronary heart disease. *J Public Health*. 2003;25(2):144-153.
13. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. *Arch Intern Med*. 2011;171(16):1441-1453.
14. de Barra M, Scott CL, Scott NW, et al. Pharmacist services for non-hospitalised patients. *Cochrane Database Syst Rev*. 2018;9:1-208.
15. Tan EC, Stewart K, Elliott RA, George J. Pharmacist services provided in general practice clinics: a systematic review and meta-analysis. *Res Social Adm Pharm*. 2014;10(4):608-622.
16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj*. 2009;339(jul21 1):b2700.
17. Methodology for JBI Mixed Methods Systematic Reviews. Available at: https://wiki.joannabriggs.org/display/MANUAL/JBI+Reviewer%27s+Manual.
18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev*. 2016;5(1):210-210.
19. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*. 2011;343(oct18 2):1-9.
20. Ayadurai S, Sunderland VB, Tee LBG, Md Said SN, Hattingh HL. Structured tool to improve clinical outcomes of type 2 diabetes mellitus patients: a randomized controlled trial. *J Diabetes*. 2018;10(12):965-976.
21. Choe H, Mitrovich S, Dubay D, Hayward R, Krein S, Vijan S. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. *American Journal of Managed Care*. 2005;11(4):253-260.
22. Gilani F, Majumdar SR, Johnson JA, et al. Adding pharmacists to primary care teams increases guideline-concordant antiplatelet use in patients with type 2 diabetes: results from a randomized trial. *Annals of Pharmacotherapy*. 2013;47(1):43-48.
23. Heisler M, Hofer TP, Schmittdiel JA, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial. *Circulation*. 2012;125(23):2863-2872.
24. Jameson J, Baty P. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. *American Journal of Managed Care*. 2010;16(4):250-255.
25. Ladhani NN, Majumdar SR, Johnson JA, et al. Adding pharmacists to primary care teams reduces predicted long-term risk of cardiovascular events in type 2 diabetic patients without established cardiovascular disease: results from a randomized trial. *Diabet Med*. 2012;29(11):1433-1439.
26. Margolis KL, Asche SE, Bergdall AR, et al. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control a cluster randomized clinical trial. *JAMA– Journal of the American Medical Association*. 2013;310(1):46-56.
27. Margolis KL, Asche SE, Bergdall AR, et al. A successful multifaceted trial to improve hypertension control in primary care: why did it work? *J Gen Intern Med*. 2015;30(11):1665-1672.
28. Mourao AOM, Ferreira WR, Martins MAP, et al. Pharmaceutical care program for type 2 diabetes patients in Brazil: a randomised controlled trial. *International Journal of Clinical Pharmacy*. 2013;35(1):79-86.
29. Neto PR, Marusic S, de Lyra Junior DP, et al. Effect of a 36-month pharmaceutical care program on the coronary heart disease risk in elderly diabetic and hypertensive patients. *J Pharm Pharm Sci*. 2011;14(2):249-263.

30. Obreli-Neto PR, Marusic S, Guidoni CM, et al. Economic evaluation of a pharmaceutical care program for elderly diabetic and hypertensive patients in primary health care: a 36-month randomized controlled clinical trial. *Journal of Managed Care and Specialty Pharmacy*. 2015;21(1):66-75.
31. Okamoto MP, Nakahiro RK. Pharmacoeconomic evaluation of a pharmacist-managed hypertension clinic. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2001;21(11):1337-1344.
32. Rothman RL, Malone R, Bryant B, et al. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *American Journal of Medicine*. 2005;118(3):276-284.
33. Rothman R, So S, Shin J, et al. Labor characteristics and program costs of a successful diabetes disease management program. *American Journal of Managed Care*. 2006;12(5):277-283.
34. Scott DM, Boyd ST, Stephan M, Augustine SC, Reardon TP. Outcomes of pharmacist-managed diabetes care services in a community health center. *American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists*. 2006;63(21):2116-2122.
35. Simpson S, Majumdar S, Tsuyuki R, Lewanczuk R, Spooner R, Johnson J. Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2011;34(1):20-26.
36. Simpson SH, Lier DA, Majumdar SR, et al. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with type 2 diabetes: results from a randomized controlled trial. *Diabet Med*. 2015;32(7):899-906.
37. Sookaneknun P, Richards RM, Sanguansermsri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. *Annals of Pharmacotherapy*. 2004;38(12):2023-2028.
38. Tahaineh L, Albsoul-Younes A, Al-Ashqar E, Habeb A. The role of clinical pharmacist on lipid control in dyslipidemic patients in north of Jordan. *International Journal of Clinical Pharmacy*. 2011;33(2):229-236.
39. Villa LA, Von Chrismar AM, Oyarzún C, Eujenín P, Fernández ME, Quezada M. Pharmaceutical care program for dyslipidemic patients at three primary health care centers: impacts and outcomes. *Lat am J Pharm*. 2009;28(3):415-420.
40. Vivian EM. Improving blood pressure control in a pharmacist-managed hypertension clinic. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2002;22(12):1533-1540.
41. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Technical Bulletin*. 1999;8(47):15-17.
42. Santschi V, Chiolero A, Paradis G, Colosimo AL, Burnand B. Pharmacist interventions to improve cardiovascular disease risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Care*. 2012;35(12):2706-2717.
43. Pousinho S, Morgado M, Falcao A, Alves G. Pharmacist interventions in the Management of Type 2 diabetes mellitus: a systematic review of randomized controlled trials. *J Manag Care Spec Pharm*. 2016;22(5):493-515.
44. Jalal ZS, Smith F, Taylor D, Patel H, Finlay K, Antoniou S. Pharmacy care and adherence to primary and secondary prevention cardiovascular medication: a systematic review of studies. *European Journal of Hospital Pharmacy*. 2014;21(4):238-244.
45. Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. *Clin Ther*. 1993;15(6):1121-1132. discussion 1120
46. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet (London, England)*. 2002;360(9349):1903-1913.
47. American Diabetes Association. Implications of the United Kingdom prospective diabetes study. *Diabetes Care*. 2002;25(suppl 1):s28-s32.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Alshehri AA, Jalal Z, Cheema E, Haque MS, Jenkins D, Yahyouche A. Impact of the pharmacist-led intervention on the control of medical cardiovascular risk factors for the primary prevention of cardiovascular disease in general practice: A systematic review and meta-analysis of randomised controlled trials. *Br J Clin Pharmacol*. 2020;86:29–38. https://doi.org/10.1111/bcp.14164